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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,130	11/21/2001	Richard W. Titball	3974-3	1328

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,130	TITBALL ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-6-04 has been entered.

Applicants amendment filed 5-6-04 has been entered. Claims 32-38 have been canceled. Claims 39-44 have been added. Claims 39-44 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 39-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein at least one of said first lipase component or said second lipase component is an N-terminal recombinant *Clostridium perfringens alpha-toxin* (N-CPAT) and a C-terminal recombinant *Clostridium perfringens alpha-toxin* (C-CPAT)," in claim 39 is vague and renders the claim indefinite. It is unclear how **a** first lipase component or **a** second lipase component can be an N-terminal recombinant *Clostridium perfringens alpha-toxin* (N-CPAT) **and** a C-terminal recombinant *Clostridium perfringens alpha-toxin* (C-CPAT) at the same time. It is unclear whether at least one of the first and second lipase components is a C-CPAT or N-

CPAT, or when the first lipase component is C-CPAT then the second lipase component is N-CPAT or vice versa, or otherwise. Claims 42-44 depend on claim 39 but fail to clarify the indefiniteness.

The phrase "capable of" in claims 40 and 41 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "capable of". It is unclear to what extent is "capable of". The specification fails to specifically define "capable of".

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 39-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claims 39-44 are directed to a pharmaceutical package comprising a first container and a second container, said first container comprises an antibody conjugated to a first lipase component having a first lipase activity, and said second container comprises a liposome containing at least one pharmaceutically active compound and a second lipase component having a second lipase activity, and said first lipase component and second lipase component reconstitute to form a third lipase component having greater lipase activity than the sum of said first and second lipase activities, wherein said first and second lipase components can be N-

CPAT or C-CPAT. Claim 40 specifies the first lipase component is an N-CPAT and the second lipase component is a C-CPAT. Claim 41 specifies the second lipase component is an N-CPAT and the first lipase component is a C-CPAT. Claims 42 and 43 specify the antibody specifically binds to an antigen, an antigen presenting cell, such as a tumor cell, and a nucleotide sequence.

The specification of the present application discloses the enhanced killing of HeLa cells using anti-CEA-phospholipase C conjugate in conjunction with drug liposomes *in vitro*. A pharmaceutical package is a package which implies *in vivo* applicability such that therapeutic effects against a disease or a disorder are obtained. The claims read on a therapy of using a reconstituted lipase activity by combining first and second lipase components *in vivo* to form a third lipase component, having lipase activity greater than the sum of the first and second lipase activities, so as to lyse a liposome and release a pharmaceutical compound, including chemotherapeutic drugs, anti-inflammatory agents, anti-fungal agents, anti-malaria agents, a polynucleotide sequence, and a protein, from said liposome for the treatment of a particular disease or disorder in vivo. The claims encompass using a pharmaceutical package for gene therapy, protein therapy, antibody therapy and organic compound therapy *in vivo*.

The specification fails to provide adequate guidance and evidence for how to administer the claimed pharmaceutical package containing an antibody-lipase complex and a liposome comprising a pharmaceutical agent, such as a small organic molecule, a polynucleotide sequence, or a protein, via various administration routes such that the antibody reaches target site in vivo and sufficient pharmaceutical agent is released from the liposome so as to provide therapeutic effect for the treatment of a particular disease or disorder *in vivo*. The specification also fails to provide an adequate guidance for the correlation of the pharmaceutical agent with a specific

disease or a disorder such that said pharmaceutical agent could provide therapeutic effects for said specific disease or disorder *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of

expression and immune responses to vectors and/or gene products" (e.g. abstract). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). Similarly, the delivery route of a protein or an antibody, the amount and stability of the protein or antibody present at the targeted site, and the uptake of the protein or antibody by the targeted cells and its activity within the targeted cells all determine the efficiency of the claimed pharmaceutical package for providing therapeutic effect in vivo.

The cited Cannon and Hui reference (submitted in the amendment filed 10-30-03) states that "[T]he route of administration should be chosen carefully when using an antibody-drug conjugate for therapy. The conjugate have high molecular weight, are often unstable in vivo (due to both proteolysis of the antibody portion and to lability of the antibody-drug linkage) and are expensive." (e.g. p. 128) and the degree of advantage of the intraarterial injection over intravenous administration of immunoconjugate depends on the pharmacokinetics of the immunoconjugate, the blood flow through the target tissue, and other factors (e.g. p. 129, second paragraph). "Reports of intramuscular or subcutaneous (other than local or intratumoral) administration of immunoconjugates are scarce. The lower systemic levels that would result from these routes of administration would be especially detrimental for immunoconjugates, because of their high molecular weight and resulting slower transport from subcutaneous or intramuscular depots into the bloodstream. The inherent instability of the immunoconjugate due to proteolysis or lability of the antibody-drug linkage could make this delay in transport into the vascular system a sever problem for intramuscular or subcutaneous injection." (e.g. p. 130). Cannon and Hui also reports that "the choice of route of administration (intravenous,

intraarterial, intratumoral, intraperitoneal, subcutaneous, or intramuscular) depends on the particular disease being treated and on the properties of the immunoconjugates (e.g. stability, specificity, toxicity, and pharmacokinetics), and the choice must be made for each indicidual case.", and the effective use of other nonsystemic routes of administration for immunoconjugates is doubtful (e.g. p. 131). "The route of administration is also important to the in vivo fate of liposomal targeting systems." (e.g. p. 133). Thus, the administration route, the molecular weight of the immunoconjugates, and the particular disease treated play important roles in providing sufficient immunoconjugates to the target cells in vivo.

The claims encompass the use of a pharmaceutical package comprising two containers comprising an antibody-lipase complex and a lipase-liposome having pharmaceutical compounds to provide therapeutic effect for a particular disease or disorder in vivo. However, the specification fails to provide at least one enabling disclosure of delivery of the claimed pharmaceutical package containing two containers to a subject via any administration route such that sufficient pharmaceutical compound is released at the target site so as to provide therapeutic effect for a particular disease or disorder in vivo.

Further, since the two containers in the pharmaceutical package are delivered to the target site at the same time the specification fails to provide adequate guidance and evidence for how and when the first lipase component and the second lipase component are reconstituted to form the third lipase component in vivo. If the first lipase component and the second lipase component are reconstituted even before reaching the target site, the pharmaceutical compound within the liposome would be released prematurely and would likely not be able to reach the target site so as to provide therapeutic effect in vivo. There is no evidence of record that the first

lipase component and the second lipase component, which are within the same pharmaceutical package, are reconstituted to form the third lipase component only when they reach the target site and said third lipase component lyse liposome to release the pharmaceutical compound to provide therapeutic effect in vivo. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed pharmaceutical package for delivery of a pharmaceutical compound, including chemotherapeutic drugs, anti-inflammatory agents, anti-fungal agents, anti-malaria agents, a polynucleotide sequence, and a protein, for the treatment of a particular disease or disorder in vivo.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the working examples provided, and the breadth of the claims that it would require a skilled artisan at the time of the invention to engage in undue experimentation to practice over the full scope of the invention claimed.

Applicants cite scientific literature, i.e. Cannon and Hui, 1990, that describes administration of antibody therapies in as broad a manner as is claimed and the claimed invention is improvement method of antibody therapy (amendment, p. 4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection. It should be noted that the present invention is directed to a "pharmaceutical package", and the term "pharmaceutical" implies therapeutic effect in vivo. The claims encompass the use of a pharmaceutical package comprising two containers comprising an antibody-lipase complex and a lipase-liposome having pharmaceutical compounds to provide therapeutic effect for a particular disease or disorder in vivo. However, the specification fails to provide at least one enabling disclosure of delivery of the claimed pharmaceutical package containing two containers to a

subject via any administration route such that sufficient pharmaceutical compound is released at the target site so as to provide therapeutic effect for a particular disease or disorder in vivo. The specification fails to provide sufficient enabling disclosure to enable the claimed invention.

Applicants cite the response filed in the amendment of October 30, 2003, and argue that Examiner has not established that those important factors for protein or antibody therapy are required to practice the claimed invention and undue experimentation is required. Applicants also argue that clinical trials are not required by the Patent Law for demonstrating enablement (amendment, p. 5). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-6-04 and the reasons set forth above under 35 U.S.C. 112 first paragraph rejection. As discussed above, the present invention is directed to a "pharmaceutical package", and the term "pharmaceutical" implies therapeutic effect in vivo. The claims encompass the use of a pharmaceutical package comprising two containers comprising an antibody-lipase complex and a lipase-liposome having pharmaceutical compounds to provide therapeutic effect for a particular disease or disorder in vivo. Indeed, no clinical trials are required to demonstrate the enablement of the claimed invention. However, the specification fails to provide at least one enabling disclosure of delivery of the claimed pharmaceutical package containing two containers to a subject via any administration route such that sufficient pharmaceutical compound is released at the target site so as to provide therapeutic effect for a particular disease or disorder in vivo. The specification fails to provide sufficient enabling disclosure to enable the claimed invention. Therefore, the claims are not enabled.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

S Chen

SHIN-LIN CHEN
PRIMARY EXAMINER